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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,612	03/29/2000	SERGIO ABRIGNANI	0366.103	7749

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EXAMINER
WORTMAN, DONNA C

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/01/2002 20

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,612	ABRIGNANI ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,29,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,29,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 18, 2002, has been entered.

As a result of that entry, claims 7, 29 and 31 were amended, claims 27, 28, and 30 were canceled, and claim 32 was added. Claims 7, 29, 31 and 32 are pending and under examination.

The claims are drawn to a method of inhibiting binding of the E2 protein of HCV to human cells comprising administering to a patient infected with HCV an amount of a CD81 protein effective to bind HCV, where the CD81 protein can correspond to all or a portion of human CD81 that binds to HCV.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 as most recently amended is indefinite because it is not clear how much, or if, the scope of the claim is intended to be altered, since the original claim required treating an HCV infection by reducing the infectivity of the virus, and the claim as presently recited requires "inhibiting binding of the E2 protein of HCV to human cells."

The original active step read "administering to a patient a therapeutically effective amount" but it now reads "administering to a patient infected with HCV an amount of a CD81 protein effective to bind HCV." It is not clear whether "inhibiting binding" is intended to be any different from "reducing infectivity" and it is not clear whether "an amount ... effective to bind HCV" is intended to be any different from a "therapeutic amount," since it would appear that administering a CD81 protein to a patient must be intended to be of at least some benefit to the patient that is connected to the binding of HCV E2 and CD81. The metes and bounds of the claims as presently recited are unclear.

Claim 7 is also indefinite because it lacks language that clearly correlates the outcome of the active step of the claim, "administering to a patient infected with HCV ...", with the preamble; the preamble recites "A method of inhibiting binding of the E2 protein of HCV to human cells."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 29, 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, essentially for reasons already of record. The specification does not teach that administration of a CD81 protein that binds HCV in fact is of any therapeutic value or benefit to a human subject. The specification at page

4 speculates that the protein or its functional equivalent may have a therapeutic effect. Rice (Hepatology 29:990-992, 1999, of record), in an article commenting on Pileri et al., Science 282:938-941, 1998, of record, points out that merely blocking or preventing HCV E2-CD81 interaction may or may not be of therapeutic value. (See, e.g., Rice, paragraph bridging pages 990-991). [Note that the Examiner's previous attribution of this reference to "Rice" was, in fact, correct.] Petracca et al. (Journal of Virology 74(10):4824-4830, 2000, of record) disclose that internalization of ligands by CD81 is rather inefficient and that it appears that certain hepatoma lines bind HCV in the absence of CD81, illustrating that mere knowledge of the association of CD81 and HCV is not sufficient to support predictability in treating HCV infection in a patient by administering a CD81 protein. One of skill in the art requires more than speculation and indeed requires some factual evidence that a beneficial effect to a human patient is actually obtained by administration to a human of a CD81 protein. In the absence of any such factual evidence, the specification cannot be said to enable one skilled in the art to use the invention as claimed.

Applicant has previously argued (1) that it has been confirmed that CD81 binds to a properly folded HCV E1E2 heterodimer that retains native conformation and has submitted an Abstract of an article by Lambot et al. in support, which article is stated to be evidence that the CD81 EC2 loop binds HCV. Applicant has argued (2) that Petracca et al., of record, supports Applicant's position regarding therapeutic efficacy since Petracca et al. demonstrates that CD81 is a cellular receptor for HCV and binds HCV E2 with high affinity, and Applicant contends (3) that the present methods only

require that HCV bind to the CD81 EC2 loop, which would leave less circulating virus and serve to decrease viral load. Applicant asserts (4) that using a CD81 protein that binds circulating HCV eliminates or reduces the amount of available virus for interacting with any cell surface receptor, including CD81. Applicant has submitted an Abstract of an article by Kishikawa et al. in support of the assertion (5) that reducing viral load is desirable since HCV viral load is correlated with the likelihood of developing hepatocellular carcinoma. Applicant has stated (6) that "even if all HCV is not available to bind administered CD81, a beneficial result can still be obtained." Applicant has pointed out (7) that the possibility that the claims may read on inoperative embodiments is not a proper basis for a rejection under 35 USC 112, first paragraph, and has noted that Applicant is not required to establish "an unerring degree of effectiveness" of pharmaceutical compositions to be used as claimed.

Applicant's arguments have been considered but not found persuasive. With respect to points (1), (2), and (5), above, it is agreed, respectively, that CD81 EC2 binds to HCV E2 in its native conformation; that cellular CD81 binds to HCV; and that reducing HCV viral load would be desirable. With respect to point (3) the claims remain drawn to a pharmaceutical or treatment method, since claim 7 recites "administering to a patient ...". Addressing point (4), there remains no factual evidence of record that administering to a patient a CD81 protein that binds circulating HCV would eliminate or reduce the amount of available virus for interacting with any cell surface receptor. Attorney's argument cannot substitute for evidence, and there is no evidence that concerns the *in vivo* fate of circulating HCV that is bound to soluble CD81. With respect

to (6), Applicant's assertion that "even if all HCV is not available to bind administered CD81, a beneficial result can still be obtained" is speculation and, as pointed out above, is not supported by factual evidence of a beneficial result. Addressing point (7), it is recognized that the possibility that the claims may read on inoperative embodiments is not a proper basis for a rejection under 35 USC 112, first paragraph, and it is recognized that Applicant is not required to establish "an unerring degree of effectiveness" of pharmaceutical compositions; however, the specification must enable one of skill to practice the invention throughout the scope of the claims, without undue experimentation, and with a reasonable expectation for success. Enablement for a method of using a protein as a pharmaceutical as claimed requires at least some factual basis for concluding that the *in vitro* results disclosed for CD81 protein can be extrapolated, with a reasonable expectation for success, to an *in vivo* benefit to a human patient.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:30-5:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw
September 29, 2002